# Modern Concepts of Cardiovascular Disease

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## PULMONARY HYPERTENSION*

### DEFINITION

Pulmonary hypertension literally implies a pulmonary blood pressure above the upper limit of normal, which is usually given as 30/15 mm. Hg. In practice, however, it may be taken to mean a pressure above 50/25 mm. Hg, for at levels lower than this it cannot be recognized clinically and has no adverse consequences, however caused. In severe cases, the pulmonary blood pressure is more or less at systemic level, but rarely in excess of 150 mm. Hg.

### CLASSIFICATION

There are three basic types of pulmonary hypertension:

1. Passive, due to a high pulmonary venous pressure.
2. Hyperkinetic, due to an increased pulmonary blood flow.
3. Vaso-occlusive, due to closing up of the vascular pathways through the lung at capillary, arteriolar, or arterial levels, however caused. There are three important subgroups of this third type:

*Obstructive*—due to agents which block the circulation from outside or inside the wall of the vessel.

*Obliterative*—due to a reduction of the pulmonary vascular capacity from structural disease of the vessels themselves.

*Vasoconstrictive*—due to functional contraction of the muscular arteries.

There are two other descriptive terms which must be mentioned here:

*Polygenic pulmonary hypertension* means that several of the above causes are operating together.

*Reactive pulmonary hypertension* is a term that may be used with advantage when it is desired not to beg the question of mechanism. This will be discussed later in relation to mitral stenosis and intracardiac shunts.

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### PASSIVE PULMONARY HYPERTENSION

#### Etiology

Passive pulmonary hypertension is caused by any condition that raises the pulmonary venous pressure sufficiently, *e.g.*, left ventricular failure, mitral valve disease, myxoma of the left atrium, cor triatriatum, multiple pulmonary venous thrombosis or stenosis, and total anomalous pulmonary venous drainage into a stenosed vessel joining the superior or inferior vena cava.

#### Physiology

In cases of critical mitral stenosis, the left atrial pressure averages about 25 mm. Hg at rest, representing a rise of about 20 mm. Hg above normal. If the cardiac output is unchanged, then the pulmonary artery pressure must rise by an equivalent amount, *i.e.*, from a mean of about 15 to 35 mm. Hg, or to a level of around 50/25 mm. Hg. On exercise, the left atrial pressure may rise to as much as 50, or even 60 mm. Hg, and if the cardiac output then doubles, the pulmonary artery pressure would be of the order of 100/50 mm. Hg. Under appropriate conditions, therefore, passive pulmonary hypertension may be of no mean order.

#### Clinical Features

Clinically, however, passive pulmonary hypertension rarely influences the symptoms, physical signs, and course of the disease that causes it. In mitral stenosis, for example, the symptoms are those associated with a high pulmonary venous pressure, *e.g.*, breathlessness, attacks of pulmonary edema, or paroxysmal nocturnal dyspnea, orthopnea, and hemoptysis. The physical signs are those of critical mitral stenosis. The electrocardiogram may show a little right ventricular preponderance, but not very much. Although the x-ray may show a rather conspicuous pulmonary artery, the chief features are those of interstitial edema of the lung and dilatation of the left atrium.




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## REACTIVE PULMONARY HYPERTENSION IN MITRAL STENOSIS

### Frequency

In a consecutive series of 500 cases of critical mitral stenosis studied by the author,[1] the pulmonary artery pressure was raised disproportionately to the left atrial pressure, owing to an increased pulmonary vascular resistance in 28 per cent. In 16 per cent, the resistance lay between 5 and 10 units (400-800 dynes sec./cm.$^5$) and in 12 per cent it was over 10 units and usually more or less at systemic level.*

### Etiology

These extreme cases represent a special kind of reaction to passive pulmonary hypertension. The obvious suggestion that the reaction was structural, and represented organic vascular disease secondary to passive pulmonary hypertension over a long period of time was denied by the average age of these patients and by their characteristic life histories. Some of the most florid cases occurred in young women in the early twenties, and 80 per cent of the group gave no earlier history of pulmonary congestive symptoms. Moreover, the remarkable fall in resistance that usually follows technically successful valvotomy is incompatible with advanced degenerative vascular disease. That a powerful vasoconstrictive factor is present in the majority of these cases can be demonstrated by injecting acetylcholine into the pulmonary artery, when the pulmonary vascular resistance may be halved. Simultaneously, the pulmonary artery pressure falls while the cardiac output and left atrial pressure rise.[2] Thus it is believed that in susceptible individuals, passive pulmonary hypertension excites a functional vasoconstrictive reaction on the part of the muscular arteries, which intensifies and perpetuates the hypertension. Structural obliterative vascular disease is a later and secondary consequence of the very high pressures that are then maintained. In the most advanced cases, this structural disease is irreversible, and the pulmonary vascular resistance fails to fall, both on injecting acetylcholine and after technically successful valvotomy.

### Clinical Features

These patients complain of symptoms referable to a low cardiac output rather than to a high pulmonary venous pressure. Thus fatigue and edema are the rule instead of hemoptysis, pulmonary edema, paroxysmal cardiac dyspnea and orthopnea.

The physical signs are characterized by peripheral cyanosis, cold extremities, a small pulse, a prominent *a* wave in the jugular pulse, a powerful heave over the right ventricle, right atrial gallop, a loud pulmonary ejection click, sharp accentuation of the pulmonary component of the second sound and perhaps a pulmonary diastolic murmur. The auscultatory signs of mitral stenosis are frequently damped and occasionally missing altogether, partly because the large right ventricle displaces the small left ventricle posteriorly, so that mitral events cannot readily be auscultated from the anterior part of the chest, and partly because the left atrial pressure and mitral blood flow are lower than they should be for the degree of stenosis present. It should be understood that the high pulmonary vascular resistance lowers the cardiac output and so protects the pulmonary venous system from developing really high pressures.

The electrocardiogram usually shows a conspicuous P pulmonale and strong right ventricular preponderance. Skiagrams show considerable dilatation of the pulmonary artery, at least moderate enlargement of the right ventricle and atrium, less enlargement of the left atrium than might be expected from the degree of stenosis present, and relatively little "pulmonary venous congestion" or interstitial edema of the lung.

### Course and Treatment

Pulmonary artery thrombosis is a common and dangerous complication in these cases and should be prevented by anticoagulant therapy until valvotomy can be undertaken. Mitral commissurotomy should be undertaken as soon as these cases are recognized, for if it is left too late, secondary changes in the muscular pulmonary arteries may prove irreversible.

## HYPERKINETIC PULMONARY HYPERTENSION

In normal subjects, increases of pulmonary blood flow up to three times normal are countered by reductions of resistance down to one-third normal, so that the pulmonary blood pressure does not rise. Once maximum vasodilatation has been achieved, however, the resistance can fall no more and any further increase of flow must result in a rise of pulmonary blood pressure. This is hyperkinetic pulmonary hypertension. It will be appreciated that if the resistance fails to fall in the face of an increasing flow, and remains, say, at 2 units (160 dynes sec./cm.$^5$), then a threefold increase of flow, *i.e.*, about 18 liters per minute, must result in a pulmonary blood pressure of

* (1) $\dfrac{\text{Mean pulmonary artery pressure (mm. Hg) minus mean left atrial pressure (mm. Hg)}}{\text{Cardiac output (liters/minute)}} = \text{units of pulmonary vascular resistance}$

(2) Units of pulmonary vascular resistance $\times 80 =$ resistance in dynes sec./cm.$^5$

around 50/25 mm. Hg (mean 36 mm. Hg). Relatively slight increases of resistance result in marked pulmonary hypertension in the face of high flows. Hyperkinetic pulmonary hypertension approaching systemic level implies a slight rise of resistance, for otherwise these high pressures could not be attained. In atrial septal defect, high pulmonary blood flows are usually associated with low resistances and a normal pulmonary artery pressure; in ventricular septal defect and patent ductus, flows of similar magnitude are usually associated with a slight rise of resistance and hyperkinetic pulmonary hypertension.

## REACTIVE PULMONARY HYPERTENSION IN POTENTIALLY HYPERKINETIC CASES

### Definition

This is the Eisenmenger syndrome,[3] which may be defined as severe pulmonary hypertension, due to a high pulmonary vascular resistance (over 10 units), associated with reversed or bidirectional shunt through a large communication between the two circulations at aortopulmonary, ventricular, or atrial level.

### Etiology

The nature of the reaction is believed to be as follows: In the collapsed unventilated lung of the fetus, the hypertrophied, constricted, and sharply kinked muscular pulmonary arteries offer a fantastic resistance to flow, calculated to be of the order of 500 to 1000 units (40,000-80,000 dynes sec./cm.[5]). At birth, and closely associated with expansion of the lung, the resistance falls quickly to around systemic level, owing to straightening out of the muscular arteries, relaxation from breathing oxygen, and passive dilatation resulting from blood flowing through the vessels. After a few hours, the resistance falls below systemic level, and results in a direct aortopulmonary shunt through the still patent ductus. This hyperkinetic factor maintains the pulmonary blood pressure at aortic level. When the duct closes, this hyperkinetic factor is removed and the pulmonary blood pressure falls sharply. Further release of vasoconstrictor tone in response to the falling pressure encourages the process and gradual structural involution of the hypertrophied muscular arteries follows, so that by the end of the third month the pulmonary vasculature acquires the adult anatomical and physiological arrangement.[4]

If, however, the ductus fails to close and leaves a sufficiently large aortopulmonary communication, a potentially more or less unlimited hyperkinetic factor maintains the pulmonary artery pressure at systemic level. In the presence of this high pressure, a significant degree of vasoconstrictor tone is maintained by the muscular pulmonary arteries and structural involution fails to take place, so that a high pulmonary vascular resistance is perpetuated. After a little while, a stable state is reached in which the pulmonary vascular resistance is more or less at systemic level and the shunt through the patent ductus is potential rather than real. Under these circumstances, the Eisenmenger reaction is set up at or shortly after birth. During the next two years, structural changes develop in the intima of the muscular arteries which tend to increase the resistance further and gradually take it above systemic level so that the shunt reverses. Cyanosis then appears in the lower extremities.

A very similar physiological situation occurs when there is a sufficiently large communication between the two ventricles. That it does not do so in the great majority of cases of large atrial septal defect is attributed to the fact that the filling resistances of the two ventricles are virtually the same in the new-born babe, owing to relative hypertrophy of the right ventricle, so that a significant interatrial shunt cannot occur at this time no matter how large the defect. Involution of the muscular pulmonary arteries is much more rapid than involution of the right ventricle, so that by the time an appreciable shunt occurs from left to right atrium, the pulmonary vascular resistance is already normal and increases of pulmonary blood flow are then countered by a further fall in resistance as in the adult state.[3]

The Eisenmenger reaction may be associated with patent ductus, aortopulmonary septal defect, persistent truncus, transposition or corrected transposition with ventricular septal defect, single ventricle, ventricular septal defect, persistent ostium primum, single atrium, atrial septal defect and total or hemianomalous pulmonary venous drainage into the right side of the heart.

When the communication between the two circulations is at atrial level, the Eisenmenger reaction is nearly always acquired, the chief factors concerned being failure of the pulmonary vascular resistance to fall low enough to prevent slight pulmonary hypertension from increased flow, repeated respiratory infection, pulmonary thrombosis and pulmonary embolism, particularly associated with pregnancy.

### Clinical Features

In a typical case of Eisenmenger's complex (shunt at ventricular level) slight to moderate effort intolerance and slight central cyanosis and clubbing date from infancy.

Examination reveals a normal pulse, venous pressure, and blood pressure. The left ventricle is usually impalpable, but there is a slight lift over the right ventricle and pulmonary artery. On auscultation, there is a soft pulmonary ejection murmur following a loud ejection click, and a single or closely split second heart sound with marked accentuation of the pulmonary component. Pulmonary incompetence is common.

The electrocardiogram may show any grade of right ventricular preponderance.

X-rays show conspicuous dilatation of the pulmonary artery, slight enlargement of the right side of the heart, and pulmonary vascular markings which may be a little heavy, more or less normal, or slightly reduced.

While it is easy enough to make a diagnosis of Eisenmenger's syndrome at the bedside, it is far from easy to determine the exact anatomical lesion present, or even the level of the shunt.

Patent ductus, however, is characterized by lack of symptoms (because hypoxia is mostly confined to the legs), differential cyanosis and a split second heart sound that widens normally on inspiration. When the shunt is at ventricular level, symptoms are more marked and date from infancy, central cyanosis is obvious on effort and the second heart sound is single or very closely split. When the shunt is at atrial level, the Eisenmenger situation usually develops in adult life, so that cyanosis is late. The most characteristic distinguishing physical sign is a widely split second heart sound which does not vary with respiration.

It should be clearly understood that none of the characteristic murmurs of patent ductus, ventricular septal defect, or atrial septal defect are present in the Eisenmenger syndrome. This applies as much to secondary mitral or tricuspid filling murmurs as it does to the continuous murmur of patent ductus and the Roger murmur of ventricular septal defect.

### Hemodynamic Data

1. The pulmonary artery pressure is the same as the systemic pressure unless the shunt is interatrial, when it is usually lower by an average of 27/34 mm. Hg.

2. The pulmonary blood flow ranges between 2 and 7 liters per minute.

3. The pulmonary/systemic flow ratio averages close to unity.

4. The pulmonary vascular resistance usually lies between 12 and 30 units, and averages around 20 units (1600 dynes sec./cm.$^5$).

5. Samples show a bidirectional shunt in 85 to 90 per cent of cases in which the communication is interatrial or interventricular; with patent ductus the shunt is wholly reversed in over half the cases.

6. The magnitude of the direct shunt is such as to increase the oxygen saturation of samples from the appropriate chamber by 5 to 20 per cent (average 12 per cent).

7. The arterial oxygen saturation in the femoral artery averages 80 per cent, whatever the nature of the defect.

8. Differential oxygen desaturation between right brachial and femoral samples is pathognomonic of patent ductus and is found in practically all such cases; the difference averages 12 per cent.

9. One of the most reliable ways of demonstrating the site of a reversed shunt is by selective dye concentration curves.

10. Selective angiocardiograms and retrograde aortograms may be equally revealing.

### Necropsy Data

1. The defect is always large, measuring between 0.7 and 1.5 cm. across with patent ductus, and between 1.5 and 3 cm. across with ventricular septal defect.

2. Heath[5] has recently discovered that sections of the root of the pulmonary artery show long, closely packed elastic fibers, like those in the aorta, when the defect is aortopulmonary or interventricular; with atrial septal defect the elastic fibers in the pulmonary artery are short, broken up, and relatively widely separated, as in the normal adult pulmonary artery. Since the elastic fibers in the root of the pulmonary artery in the new-born babe also resemble those in the aorta, Heath believes that this arrangement provides good evidence that the pulmonary hypertension of the Eisenmenger syndrome always dates from birth when associated with aortopulmonary or interventricular defects, but is nearly always acquired in cases with atrial septal defect.

3. The muscular pulmonary arteries are thickened and resemble those of the fetus, as emphasized by Civin and Edwards.[6] Small thick-walled vessels may represent larger vessels in a state of vasoconstriction.[7]

4. During the first year or two of life, the intima usually remains normal; subsequently, however, progressive intimal fibrosis develops.

5. Sooner or later, secondary thrombotic lesions occur.

### Course and Prognosis

The majority of cases change very little in childhood and adolescence, but serious deterioration usually sets in during the third decade. This is often precipitated by an hemoptysis secondary to pulmonary infarction resulting from thrombosis of one of the larger branches of the pulmonary artery. This increases the pulmonary vascular resistance and encourages right ventricular failure. The average age of death is 33. A large hemoptysis is the immediate cause of death in about a quarter of the cases; ill-advised surgical interference accounts for another quarter; about 15 per cent die abruptly, presumably from ventricular fibrillation, and 20 per cent succumb to heart failure. Relatively rare causes include bacterial endocarditis and cerebral abscess.

### Treatment

On theoretical grounds, it would seem reasonable to repair the defect during the first two years of life, before irreversible changes in the pulmonary vasculature have taken place. The muscular pulmonary arteries would then be expected to involute and reactive pulmonary vasoconstriction to abate, the hyperkinetic factor having been eliminated. To repair the defect later is to court disaster by removing the safety valve in the pulmonary circulation. Permanent anticoagulant therapy, from the age of 20 onwards, may help to prevent secondary thrombotic lesions.

Dammann and Ferencz[8] have suggested creating artificial pulmonary stenosis to encourage the muscular arteries to involute, and to follow this up by full repair a year or two later.

## VASO-OCCLUSIVE PULMONARY HYPERTENSION

### 1. Obstructive

The best example of obstructive pulmonary hypertension is multiple or recurrent thrombo-embolism. If a sufficiently high pulmonary blood pressure is maintained long enough, whether induced purely by mechanical obstruction or partly by secondary vasoconstriction, reactive structural changes develop in the media and intima of the muscular pulmonary arteries, resulting in a form of irreversible pulmonary hypertension very difficult to distinguish from the later stages of primary pulmonary hypertension.

If diagnosed and treated energetically within three months of the onset, however, these cases may be cured. Treatment must be continued for several months and includes anticoagulants, bed rest, and a variety of agents designed to lower the cardiac output and relieve pulmonary vasoconstriction. Such agents include oxygen, sedatives, a low-sodium regime, reserpine, priscoline, and aminophylline. Ganglionic blocking agents may also be tried.

### 2. Obliterative Pulmonary Hypertension

Obliteration of at least two-thirds of the pulmonary vascular capacity from structural disease of the pulmonary blood vessels may result from schistosomiasis, lupus, and perhaps other forms of arteritis. More commonly, however, obliterative pulmonary hypertension results from destruction of capillaries and arterioles from emphysema or diffuse interstitial fibrosis of the lungs. Severe chronic pulmonary hypertension of this kind is found in about 20 per cent of cases of cor pulmonale, and is neither relieved by oxygen therapy nor associated with a raised cardiac output. Acetylcholine usually fails to lower the pulmonary vascular resistance in these cases.

### 3. Vasoconstrictive Pulmonary Hypertension

In the majority of cases of cor pulmonale, however, pulmonary hypertension is transient, and is associated with attacks of bronchitis or asthma when it is due to vasoconstriction induced by alveolar hypoxia.[9] In such cases, the pulmonary vascular resistance falls sharply in response to improved ventilation, oxygen therapy, or the injection of acetylcholine into the pulmonary artery.

A vasoconstrictive reaction to pulmonary hypertension itself, however caused, may also play a part in the genesis, maintenance, and aggravation of many other forms of pulmonary hypertension. The reaction is believed to be no more than the normal physiological response of the muscular pulmonary arteries to a rise of tension within them. Its magnitude in any particular case may be estimated by measuring the fall in resistance that follows the administration of acetylcholine.

## PRIMARY PULMONARY HYPERTENSION

### Etiology

Although the cause of this condition is still unknown, it may be helpful to mention one or two facts which seem to deny a congenital or thrombo-embolic etiology:

The fall in pulmonary vascular resistance that usually follows the injection of acetylcholine tends to be of a greater order than that found in any other form of pulmonary hypertension. This provides good evidence that the disease is not congenital, for in the Eisenmenger syndrome the response to acetylcholine is uniformly negative.[3]

The second point concerns the sex factor. In primary pulmonary hypertension, the male/female sex ratio is about 1 to 5; in known cases of chronic thrombo-embolic pulmonary hypertension it is unity.

### Clinical Features

Since this is the purest form of pulmonary hypertension, a brief description of the clinical picture may not be out of place:

The patient is usually a young married woman.

There are no symptoms until the condition is fully developed. Effort tolerance is limited as much by fatigue, angina pectoris, faintness, or even syncope, as by breathlessness. There is no orthopnea. Hemoptysis is relatively rare. Sooner or later congestive failure results in abdominal discomfort and edema.

Cyanosis is either absent or peripheral. The pulse is small and the blood pressure rather low.

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A giant *a* wave in the jugular pulse and right atrial gallop are the rule. The left ventricle is impalpable, but there is an appreciable lift over the right ventricle and pulmonary artery. A loud pulmonary ejection click, sharp accentuation of the pulmonary component of a normally split second heart sound, and often a pulmonary diastolic murmur, complete the findings. In more advanced cases, tricuspid incompetence and the signs of congestive failure complicate the picture.

### Hemodynamic Data

The characteristic findings in relatively early cases include a low cardiac output, an unusually high arteriovenous oxygen difference, a pulmonary artery pressure commonly between 60/30 and 100/50 mm. Hg, a pulmonary vascular resistance between 10 and 40 units, a normal arterial oxygen saturation, normal lung function, and no shunt.

### Prognosis and Treatment

Although the natural course of this disease is death from congestive heart failure in a matter of two or three years from the time the diagnosis is first made, earlier recognition and modern treatment seem to have extended life expectancy to between five and ten years. The chief agents responsible for prolonging life appear to be permanent anticoagulant therapy to prevent thrombosis, pulmonary vasodilators such as reserpine, priscoline, and aminophylline, and modern methods of controlling heart failure.

### SUMMARY

1. Pulmonary hypertension usually implies a pressure of over 50/25 mm. Hg.

2. It may be passive (due to a high pulmonary venous pressure), hyperkinetic (due to a high pulmonary blood flow), or vaso-occlusive (due to a high pulmonary vascular resistance).

3. Vaso-occlusive pulmonary hypertension may be chiefly obstructive (from external pressure or internal thrombosis), obliterative (from destruction or occlusive disease of capillaries, arterioles or muscular arteries), or vasoconstrictive (functional).

4. Reactive pulmonary hypertension is a useful term to describe cases with a high pulmonary vascular resistance secondary to passive or hyperkinetic pulmonary hypertension.

5. Polygenic hypertension best describes cases of multiple etiology.

6. However initiated, pulmonary hypertension seems to be perpetuated and aggravated first by vasoconstriction (reversible), then by structural changes in the walls of the arteries (chiefly hypertrophy of the muscular media and endarteritis fibrosa), and finally by secondary thrombo-obstructive lesions in the lumen of the vessels.

7. The majority of cases of pulmonary hypertension are chiefly functional and reversible in their earlier stages and chiefly structural and irreversible in their later stages.

8. The magnitude of passive, hyperkinetic, and vasoconstrictive functional factors can be measured by relatively simple techniques (wedge pressure, Fick output, and acetylcholine test).

9. Operative treatment of the primary cause of any case of pulmonary hypertension is pointless and dangerous in the presence of severe, irreversible, vaso-occlusive, structural pulmonary vascular disease.

10. Permanent anticoagulant therapy may retard the downhill course of irreversible pulmonary hypertension by preventing secondary thrombo-obstructive lesions. It may be curative in subacute thrombo-embolic pulmonary hypertension.

11. The cause of primary pulmonary hypertension is still unknown.

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